PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	Group Art Unit: 1211
STEVEN C. QUAY	Examiner: G. Hollinden
Appln. No. 08/466,104	**SECOND DECLARATION OF PAMELA HILPERT, M.D., Ph.D.**
Filed: June 6, 1995	
For: PERSISTENT GASEOUS BUBBLES AS ULTRASOUND CONTRAST MEDIA	2001 Ferry Building San Francisco, CA 94111 (415) 433-4150

I, Pamela Hilpert, M.D., Ph.D., declare under the penalty of perjury that the following is true and correct:

1. I previously executed sworn statements entitled DECLARATION OF PAMELA HILPERT dated January 9, 1998 (hereinafter "FIRST HILPERT DECLARATION") in two separate, but related, Patent Office proceedings (Reexamination Nos. 90/004,656 and 90/004,657). I understand that a copy of the FIRST HILPERT DECLARATION filed in Reexamination No. 90/004,657 on U.S. Patent No. 5,573,751 is being concurrently submitted with this second declaration. I hereby affirm all of the statements made in the FIRST HILPERT DECLARATION for the purposes of the (above captioned) present patent application proceeding.

2. My relevant qualifications and background are detailed in my FIRST HILPERT DECLARATION and remain unchanged since that time.

3. In addition to the materials listed as having been reviewed in my FIRST HILPERT DECLARATION, I have reviewed the following document in preparation for providing this declaration: U.S. patent application serial number 08/466,104, i.e., the

current application in which this declaration is made (hereinafter "the Quay application").

4. As I stated in my FIRST HILPERT DECLARATION, I am the author of a paper entitled "Contrast Agents in Diagnostic Ultrasound," which was published as Chapter 3 of Volume 1 of a multi-volume text entitled, Diagnostic Ultrasound. A true and correct copy of that chapter, as published in 1991, is attached hereto as Exhibit 1. Exhibit 1 is referred to in the rest of this declaration as the "Hilpert Chapter." Prior to writing the Hilpert Chapter, I conducted a study of the state of the ultrasound contrast agent art in 1991 and summarized my findings in the Hilpert Chapter. In order to prepare the Hilpert Chapter, I reviewed at least 150 journal articles relating to ultrasound contrast agents in existence at that time. Of the journal articles I reviewed, 77 are included in the bibliography to the Hilpert Chapter.

5. My approach in preparing the Hilpert Chapter was to review and collect information which would be a complete survey of the development of then existing ultrasound contrast agents.

6. In the Hilpert Chapter I, identified five different types of agents which, in the 1991 time frame, had been recognized by researchers working on the development of ultrasound contrast agents: free gas bubbles, encapsulated gas bubbles, colloidal suspensions, lipid emulsions and aqueous solutions.

7. Based on my personal experience with the state of the art of ultrasound contrast up to and including 1991, and my review of the Quay application, I conclude that one skilled in the art of developing ultrasound contrast agents in the 1991 time frame would have readily understood from the

text of the Quay application that gases such as perfluoropropane, perfluorobutane and perfluoropentane stabilized with human protein were part of the invention disclosed. I reach this conclusion based on the following:

(1) As explained in the Hilpert Chapter, those developing contrast agents in the years leading up to 1991 were familiar with protein stabilized microbubbles of air. By way of example, in the section entitled "ENCAPSULATED GAS BUBBLES" at page 33 of the Hilpert Chapter, I reported that "(s)onication of 5% human serum albumin produces a gas-filled microbubbles that is small (3 to 5 μm) and stable enough to allow free passage through the pulmonary circulation."

(2) The Quay application discloses a number of then existing techniques for making ultrasound contrast media. Among them is making of solutions in which microbubbles were stabilized by human protein. This description appears in the Quay application under the heading: "Materials Presently Used as Contrast Enhancing Agents", and the subheading "Microbubbles" (application pages 16-17). This review of the existing contrast agents in development is consistent with the descriptions in the Hilpert Chapter and is an accurate reflection of the state of the art in 1991.

(3) The Quay application goes on to point out (under the "Brief description of the Invention", pages 20-21 of the specification) that "[t]he microbubbles can be produced using existing techniques that use ordinary air, and can be infused as in a conventional ultrasound diagnosis", and more specifically that "[u]sing existing techniques, substantially improved contrast enhancing media may

then be produced and used to improve the quality and usefulness of ultrasound imaging."

(4) The reference in the Quay application's "Brief Description of the Invention" to "existing techniques that use ordinary air" would reasonably be read by one skilled in the art as referring to the techniques described in the immediately preceding background section for preparing gas containing agents which include the description of the method of using human protein as a stabilizer for microbubbles.

I understand that the above statements were made with the knowledge that willful false statements and the like are punishable by fine and/or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statement may jeopardize the validity of the subject patent application or any patent resulting therefrom.

Executed this 31 day of July, 1998 at Torrance, California.

PAMELA HILPERT, M.D., Ph.D.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on August 3, 1998

LIMBACH & LIMBACH, L.L.P.

Dated: 08/03/98 By: _____

Name